1. Introduction

There are often many different options for improving healthcare policy or improving current practice in healthcare organizations. The optimal solution among those options, i.e., the solution that best achieves a defined goal, such as maximizing patient quality-of-life or minimizing patient waiting time for services, may not be readily apparent. Constrained optimization methods use mathematical techniques to help efficiently and systematically identify the best (optimal) of all possible solutions to a problem while considering the relevant constraints, such as budget limits or staffing capacity.

Of course, mathematically optimal solutions to all problems are not always feasible; other non-quantifiable criteria that cannot be accounted for by defined constraints have to be considered. However, optimization techniques can still be highly informative to decision makers in providing insights about optimal target solutions and the magnitude of the loss of benefit or increased costs associated with the ultimate policy choice. In healthcare, failing to identify a mathematically superior or optimal solution represents a missed opportunity to improve economic efficiency in the delivery of care and clinical outcomes for patients.

The ISPOR Optimization Methods Emerging Good Practices Task Force provided an introduction to constrained optimization methods to solve important health policy and clinical problems in its first report (Crown et al., 2017). The previous report outlined the relationship of constrained optimization methods relative to traditional health economic modeling and simulation models and identified some of the major variants of constrained optimization models, such as linear programming, dynamic programming, integer programming, and stochastic programming.

In addition, the report graphically illustrated the formulation and solution of a straightforward integer program to maximize health benefit subject to a budget constraint. Further, it explained the steps in an optimization process: 1) structuring the problem, 2) formulating the mathematical model, 3) developing the model, 4) validating the model, 5) selecting the optimization method, 6) performing the optimization and conducting sensitivity analysis, 7) reporting results, and 8) using the results for decision-making.

The principal objective of this second Optimization Task Force Report is to illustrate the application of constrained optimization methods in healthcare decision making. To identify relevant examples, we began by searching for award-winning health care papers from the Institute for Operations Research and Management Sciences (INFORMS) and the Association for European Operations Research Societies (EURO). From these papers, we then selected examples with models relevant for health economic policy or clinical decision-making. Finally, we endeavored to select papers that collectively illustrated a variety of different constrained optimization methods. The three papers that received the most votes from the task force members were selected.

In this report, two of these three papers are compared with the steps in formulating, solving, validating, reporting, and using optimization models originally published as Table 3 in the first Optimization Emerging Good Practices Task Force Report (Table 1 in this report.) The first case study illustrates the application of linear programming to determine the optimal mix of screening and vaccination strategies for the prevention of cervical cancer (Demarteau et al., 2012). The second case illustrates application of the Markov Decision Process to find the optimal strategy for treating Type-2 diabetes patients for hypercholesterolemia using statins (Denton et al., 2009). Finally, the third paper is used as an education tool. The goal is to describe the characteristics of a radiation therapy optimization problem and then invite the reader to formulate the mathematical model for solving it. This example is interesting because it lends itself to a range of possible models, including linear, non-linear, and mixed-integer programming formulations. (Detailed formulations for each model are provided in Appendix 1.)

Although we are clearly limited in the number of permutations that we can present with these three cases we hope the reader will develop a sense of the wide range of problem types that can be addressed with constrained optimization methods, as well as the variety of methods available.

2. Overview of applications of constrained optimization in health care

Constrained optimization methods are already widely used in healthcare areas such as choosing the optimal location for new facilities, making the most efficient use of operating room capacity, workforce planning, etc. They can also be instrumental in guiding clinical decision-making in actual clinical practice where health professionals and patients face constraints, such as proximity to treatment centers, health insurance benefit designs, and the limited availability of health resources.

Optimization is also beneficial for planning healthcare expenditure. An obvious example is the resource allocation problem faced by a planner with a number of investment opportunities, but a fixed budget inadequate to fund all available opportunities (Stinnett and Paltiel, 1996). Perhaps the simplest case of this is where the investment opportunities are incremental to current care, and fall into distinct categories (e.g.,

children's services, cardiovascular disease, cancer, respiratory disease and mental health) with separate budgets (as in Airoldi et al., 2014). In this situation, decisions about investments in different clinical areas can be made independently of one another. However, more commonly the health care budget needs to be allocated across different conditions. The problem of choosing the best set of investment opportunities to fund under a fixed budget constraint in order to meet an objective, such as maximizing total QALYs can be addressed as an optimization problem (Martello and Toth, 1990). Given a number of eligible interventions and a fixed budget, optimization can be used to solve resource allocation problems. In fact, the task central to health economic analysis, of evaluating whether the incremental cost-effectiveness ratio (ICER) of an intervention is below a critical threshold, can be shown to be related to budget constrained optimization. According to the theoretical definition, under a strict set of assumptions, the threshold represents the inverse of the shadow price of the budget constraint – the shadow price is defined as how much the objective (i.e. QALYs) would increase for a one-unit increase in the constraint (budget). (Weinstein and Zeckhauser, 1973; Thokala, et al, 2018).

Other resource allocation problems may be even more complicated. There may be significant and complex interactions between different investments; and there may also be other constraints such as resource constraints (e.g. staff, beds, etc) (Thokala et al 2015). For example, consider the case of allocating resources for the prevention and cure of an infectious disease such as HIV, Hepatitis C, TB, malaria, or polio (Castillo-Chavez and Feng, 1998, Juusola and Brandeau, 2015). If the planner invests in vaccination, there may be fewer cases to treat in the future (and so investment in highly capital-intensive treatment facilities may be wasted). On the other hand, vaccination is itself costly, and if the disease has a low prevalence, it may be more cost-effective to target the treatment (Lee et al., 2015). For more details on these complexities see the ISPOR Economic Evaluation of Vaccines Designed to Prevent Infectious Disease Good Practices Task Force Report (Mauskopf et al., 2018). Optimizing investment in such infectious disease programs is more complicated as they may involve making multiple runs of a state-of-the-art simulation (Marshall et al., 2015a, Marshall et al., 2015b) of the infectious disease dynamics, to plot out how the particular patterns of resource allocation perform against the objective (of minimizing the total number of cases or maximizing the probability of achieving disease eradication). For a review of mathematical approaches to infectious disease prediction and control, see (Dimitrov and Meyers, 2010).

In other settings, the critical resource(s) might not be money. For example, when allocating donated organs, (e.g., a kidney), not every kidney will be compatible with every donor. In addition, the medical condition of the eligible recipients will be different, some will be more urgent than others. In this case, the underlying problem can be categorized as a matching problem (Roth and Sotomayor, 1992; Segey et al., 2005). In matching problems, not everyone will get the best match. However, the objective with kidney

allocation is generally to ensure that as few as possible people and kidneys are left unmatched (patients without kidneys; kidneys without patients) (Bertsimas et al., 2013). Bertsimas et al., 2013 present a discussion about how to incorporate fairness in such problems. Some measures of deservingness, e.g., time on waiting list, may be incorporated in the objective function. Nevertheless, some fairness considerations may also be included as constraints, e.g., at least x % of transplants should go to patients of a certain blood type. The 2012 Nobel Prize in Economics was awarded to Shapley and Roth, in part for their work in stable matchings applied to organ donation.

Other clinical problems where optimization can be applied relate to problems of disease management, e.g., timing of the initiation of treatment, or the sequence of treatments. The promise of health gain from treatment must be balanced against reasons for holding off treatment, which may include cost, undesirable side-effects, and emergent drug resistance. It may be the case that there is an optimal stage in the disease prognosis or point in the patient's life cycle where the balance shifts from favoring non-intervention to favoring treatment. The MDP approach provides an ideal framework (Puterman, 2014) to study such problems for identifying critical initiation points. This framework has been used to analyze timing decisions in diseases as diverse as HIV, diabetes, and breast cancer (Shechter et al., 2008, Denton et al., 2009, Chhatwal et al., 2010). Optimization methods can be applied to identify the optimal treatment sequences when a large number of treatments are available--for example, in rheumatoid arthritis (Tosh et al. 2015).

Finally, constrained optimization methods have also been applied to disease diagnosis (Lee and Wu, 2009; Liberatore and Nydick, 2008), the development of optimal treatment algorithms (Ehrgott et al., 2008; Lee et al., 2008), and the optimal design of clinical trials (Bertsimas et al., 2013). Health technology assessment using tools from constrained optimization methods is also gaining popularity (Thokala et al., 2018). We also encourage the readers to refer to the first ISPOR Optimization Emerging Good Practices Task Force Report, which presented a more comprehensive overview of the different applications for which optimization techniques can be used (Crown et al., 2017).

3. Steps in an Optimization Process

Table 1 reproduces the steps of the optimization process previously presented in the initial Optimization Task Force Report. It is reproduced here to reduce the burden on the reader as the two case studies and the educational example will all be discussed in light of this framework. The primary purpose of Table 1 is to support the design of optimization studies by prompting the user to report and justify the choices made at each step of the process. It should be noted that the steps outlined in Table 1 do not need to be conducted sequentially. In fact, most of the optimization studies involve performing these steps in an iterative manner to solve the problem. Along with guiding the design of optimization studies, Table 1 can also be used to

support the critique and quality assessment of published optimization studies. The steps in Table 1 are described in detail in the text below.

Table 1. Steps in an Optimization Process

Stage	Step	Description
Modeling	Problem structuring	Specify the objective(s) and constraints, identify decision variables and parameters, and list and appraise model assumptions
	Mathematical formulation	Present the objective function(s) and constraints in mathematical notation using decision variables and parameters
	Model development	Program the model in software to estimate the objective function(s) and constraints, using decision variables and parameters as inputs
	Model validation	Ensure the model is appropriate for evaluating different combinations of decision variables and parameters
Optimization	Select optimization method	Choose an appropriate optimization method and algorithm on the basis of characteristics of the problem.
	Perform optimization/sensitivity analysis	Use the optimization algorithm to search for the optimal solution and examine the performance of the optimal solution for reasonable sets of parameters

	Report results	Report the results of the optimal solution and sensitivity analyses
	Decision making	Interpret the optimal solution and use it for decision making

Source: Crown et al. 2017, Table 3, p. 315.

Problem structuring: The first step is to determine if constrained optimization is an appropriate methodology to address the problem at hand (Rosenhead, 1996). It involves identifying if there are any quantifiable constraints and whether a specific goal can be achieved by changing some (decision) variables. This problem structuring phase should be done in consultation with the key stakeholders and decision makers to ensure that the optimization problem is appropriately specified. This will ensure that the objective functions and constraints are appropriate and get their 'buy-in' to change the decision variables in order to achieve an optimal solution. A clear textual description of the decision problem should be reported and validated with the key stakeholders and decision makers.

Mathematical formulation: This involves converting the textual description into a mathematical representation of the optimization problem. Objective function(s) and constraints need to be defined in analytical form as a function of decision variables and parameters. Note that decision variables are changed during optimization iterations in order to identify the optimal solution, while parameters remain fixed. The number and type of decision variables (e.g. continuous or discrete) as well as the parameters need to be justified. The type of objective function (i.e. single objective or multi-objective, linear or non-linear, stochastic or deterministic) and the type of estimation (i.e. analytical estimation or via simulation modelling for complex problems) need to be specified. Similarly, for constraints, the number of constraints and the type of estimation used for the constrained quantity need to be reported and justified. The sources and the values of the parameters used to estimate the objective function(s) and constraints also need to be justified. The mathematical representation of the optimization problem should be reported after validation with the key stakeholders and decision makers.

Model development: This involves programming the model in software to estimate the objective function(s) and constraints, using decision variables and parameters as inputs. It should be noted that in some instances, the analytical form of the mathematical formulation can be programmed directly i.e. the

mathematical formulation sufficiently defines the relationships between objective function(s)/constraints and decision variables/parameters. However, in other instances, a simulation model needs to be developed to estimate the objective function(s)/constraints. Models should be designed so that the objective function can be evaluated based upon the full range of possible decision variables (the feasible region or search space). The model structure and assumptions should be reported and validated with the key stakeholders and decision makers. The initial mathematical formulation and model development steps affect the specification of the particular optimization method to be applied. These steps are closely related and interdependent. This is one important reason why the steps in optimization do not always have to follow the order described in Table 1.

Model validation: Before the optimization is undertaken, the underlying model needs to be verified and validated, to ensure the robustness of the results for different analyses performed (i.e. the model is consistent with reality within tolerances). Once the model has been developed to the point where it is producing estimates, the model code also needs to be checked to ensure the model results are valid. In the case of models that represent an analytical formulation directly, this is relatively straightforward as this involves checking the specific model results used as parameters for estimating the objective function and constraints.

However, when a simulation model is used to evaluate the objective function, this would necessitate a combined approach of simulation-optimization (Lin et al., 2013, Fu, 2002) which is a bit more difficult as it involves checking the model results for all combinations of decision variables. Meta-modeling techniques (Barton 1994), i.e., modeling the simulation model outputs as functions of simulation inputs, can circumvent getting the simulation results for all variables in the parameter space. These topics are beyond the scope of this report; we suggest reviewing Sargent (2009) and Law (2006).

Modelers are encouraged to validate the model results in different parts of the decision variable space to have enough confidence that the model used is appropriate for optimization (Eddy et al., 2012; Vemer et al., 2014). This should also involve asking the key stakeholders and decision makers to check the model results for face validity.

Select optimization method: The choice of optimization method needs to be justified on the basis of the type of decision variables (i.e. continuous or discrete), and the type of objective function (i.e. single objective or multi-objective, linear or non-linear, stochastic or deterministic), and the type of constraints (i.e. single vs multiple constraints). The optimization algorithm/tool used also needs to be justified on the basis of the optimization method, as well as the estimation type (i.e. analytical formulation vs simulation

optimization) and other relevant characteristics of the model (e.g. number of decision variables or transferability of the problem to other well-known problem types). The methods and tools chosen for optimization need to be reported and justified.

Perform optimization/sensitivity analysis: This involves running the optimization model, identifying the optimal solution, and understanding the impact of alternative parameters on the optimal solution using sensitivity analyses. Settings used for the optimization, such as the convergence level required or the maximum number of iterations, need to be justified. In some problems, searching for the optimal solution might be computationally feasible, whereas in others, solving time increases to such an extent that the use of heuristics is justified.

As with decision modelling, optimization can have stochastic uncertainty in parameters and model structure. Stochastic optimization (Spall, 2005), robust optimization techniques (Gorissen, Yanıkoğlu, and den Hertog, 2015) and sensitivity analyses can be used to deal with parameter uncertainty. However, structural uncertainty needs to be dealt with by thinking about the choices throughout the optimization process. For example, is a linear program really appropriate? Are the simplifications and assumptions appropriate and to what extent is there a risk of a wrong/sub-optimal decision being reached? The choice of decision variables, parameters, constraints, and model assumptions also need to be structurally evaluated.

The optimal solution needs to be checked to identify if it is feasible and, if so, sensitivity analyses should be conducted. The optimization settings and the sensitivity analyses need to be explained to the key stakeholders/decision makers and reported in detail.

Report results: This involves specifying the values of the decision variables, objective function and constraints at the optimal solution, for the base case analyses, as well as the sensitivity analyses. The optimization results (i.e. optimal solution for the base case and sensitivity analyses) need to be reported and validated with the key stakeholders/decision makers. Also, the performance of the optimization tool/method needs to be reported, such as the time taken to identify the optimal solution, number of iterations required, and the convergence level (if applicable). These results should be reported in a manner that is understandable and interpretable by relevant stakeholders and decision makers.

Decision making: The meaning of the optimal solution should be explained to the decision makers. This involves converting the mathematical optimal solution into clear, concise plans for implementation. At this stage, the choices made at all the stages of modelling (i.e. type of model, data, assumptions) and optimization (i.e. the design, settings and assumptions) need to be validated to ensure the results of

optimization problem are plausible and consistent with decision maker objectives. Also, the possibility of amending the decision variables to the values specified by the optimization process need to be checked with the stakeholders to ensure that the implementation is feasible. To reiterate, the results of the optimization should not be used mechanistically: it is the decision makers that implement the findings, hence they should be comfortable with the methodology, data, and assumptions involved in the whole optimization process.

4. Optimization Case Studies

In this section, we consider two constrained optimization studies and compare their structure to the steps outlined in Table 1. The first case study focuses on resource allocation for the prevention/cure of infectious diseases while the second illustrates the use of constrained optimization to guide optimal treatment initiation. These cases illustrate different modeling techniques, as well as extensions of the application of constrained optimization methods beyond the typical realm of scheduling, shipping cost minimization, maximization of facility capacity, etc.

Case Study 1. Selecting a Mix of Prevention Strategies Against Cervical Cancer (Demarteau et al., 2012)

Problem Structuring

Cervical cancer is the second most common cancer in women under 35 years old in the UK. The objective of this study was to identify the optimal mix of primary and secondary prevention strategies for cervical cancer that achieves maximum reduction in cancer cases under budget and logistic constraints. The authors applied the optimization model in two countries with different healthcare organizations, epidemiology, screening practices, resource settings and treatment costs: one in the UK, and one in Brazil. They considered two cervical cancer prevention strategies against human papillomavirus (HPV):

- Primary prevention – Because an HPV infection is the most common cause of cervical cancer, HPV vaccination is a primary prevention strategy. Two HPV vaccines are currently available. Both vaccines have an efficacy of approximately 98% against the cervical cancer vaccine HPV types (HPV 16 and 18), but with a different cross-protection profile against oncogenic non-vaccine HPV-types. The implementation of vaccination varies widely among countries with regard to the strategy selection (national immunization program or individual based); the logistics (via a separately established vaccination setting or via primary healthcare); the age group targeted; and the gender selection (female only or both).

- Secondary prevention - Cytology-based screening programs have contributed to a decrease of up to 80% in the incidence and mortality of cervical cancer in countries with a well-established, organized screening program. However, despite their potential, cytology-based screening programs sometimes have a limited impact due to factors such as sensitivity of the screening method (ability of the test to correctly identify those patients with the disease), treatment failure and the level of resources required for an adequate follow-up of patients.

Four prevention strategies were evaluated: screening; vaccination; screening plus vaccination; and no prevention because these were the options available for cervical cancer prevention in the UK and Brazil at the time of the study. Only cytology-based screening was included in the model, with sensitivity estimates based on published literature. Different screening interval scenarios were explored, from every year to every 25 years (i.e. women are then screened only twice over their lifetime) with a 1-year increment between each scenario.

It was assumed that vaccination is administered at age 12 and induces lifelong protection against HPV. In total, 52 different strategies were tested for each country. These 52 strategies defined the full range of possible combinations of vaccination (not available or available) and screening interventions (not available or available with intervals between screening estimated from 1 year to 25 years in 1-year increments). The final scenarios can be listed as follows: (*scenario 1*: no screening & no vaccine; *scenario 2*: 1-year screening interval & no vaccine; *scenario 3*: 2-year screening & no vaccine; … , *scenario 26*: 25 year screening & no vaccine' *scenario 27:* no screening & vaccine; *scenario 28:* 1 year screening & vaccine; *scenario 29:* 2 year screening & vaccine ; … , *scenario 52*: 25-year screening & vaccine).

Mathematical Formulation

The optimization model used a linear programming formulation consisting of a single linear objective function and multiple linear constraints. The model was continuous, allowing fractional values for the decision variables. It was static meaning that the problem was solved once at steady state. Finally, the model was deterministic which assumed that all the outputs were known and there was no stochastic variation.

Fifty-two decision variables, x_i, each representing the proportion of the population addressed by each strategy considered, $i = 1, 2, \ldots, 52$, were used with separate identifiers for strategies involving screening and strategies involving vaccination in order to deal with screening and vaccination coverage constraints. Given the aim was to minimize the number of cervical cancer cases, the objective function was represented as the sum of the cervical cancer cases (at steady state for 100 000 women) for each strategy, CC_i, multiplied by the proportion of population receiving each strategy, x_i.

303 The linear programming formulation for the cervical cancer prevention strategy optimization is given as

$$\min \quad \sum_{i=1}^{52} CC_i x_i \tag{1}$$

$$\text{subject to} \quad \sum_{i=1}^{52} b_i x_i \leq B \tag{2}$$

(budget constraint)

$$0 \leq x_i \leq 1, \qquad for\ i = 1,2, \dots, 52 \tag{3}$$

(strategy coverage bounds)

$$\sum_{i=1}^{52} x_i = 1 \tag{4}$$

(complete population distribution)

$$\sum_{i=2}^{26} x_i + \sum_{i=28}^{52} x_i \leq Cov_1 \tag{5}$$

(screening coverage upper bound)

$$\sum_{i=27}^{52} x_i \leq Cov_2 \tag{6}$$

(vaccination coverage upper bound)

$$x_1 \leq \min(1 - Cov_1, 1 - Cov_2) \tag{7}$$

(upper bound on population with no coverage)

$$x_i \in R, \qquad for\ i = 1,2, \dots, 52 \tag{8}$$

304

305 The model has five constraints: budget, strategy coverage, total population, screening and vaccination
306 coverage limits. The first constraint is to ensure that the sum of the cost for each strategy (at steady state
307 for 100000 women), b_i, multiplied by the proportion of the population receiving each strategy, x_i, is less
308 than the overall budget constraint, B. The strategy coverage constraint ensures that the proportion of each

strategy is between 0 and 1. The complete population distribution constraint guarantees that all the 52 variables add to 1 (i.e. the sum of the proportion of the population receiving each strategy should reflect the entire population).

Also, the sum of the proportion of the population receiving strategies including screening should be less than the externally (e.g. government) imposed screening coverage limit, Cov_1. Similarly, the sum of proportion of population receiving strategies including vaccination should be less than the externally (e.g., government) imposed vaccination coverage limit, Cov_2. Note that the parameters CC_i and b_i are derived from the Markov cohort model (see details below) for each strategy i.

Model Development:

The mathematical formulation described above used the outputs of a health economic Markov cohort model (number of cervical cancer cases CC_i and total costs b_i for each strategy i) as input parameters. The Markov cohort model describes the population level natural history of cervical cancer for the evaluation of the clinical and economic consequences of different prevention strategies. The model considers a population of 100,000 women under a given prevention strategy at steady state level. The Markov model consists of following states: no HPV infection, HPV infection, cervical intraepithelial neoplasia (CIN) stages, cancer, and death (both cancer and non-cancer related).

Once patients are infected with HPV, individuals can progress and regress from HPV infection and CIN stages. Vaccination is assumed to reduce the HPV infection rates, and detection through screening provides the possibility of the treatment of CIN. Overall vaccine efficacy in the UK and Brazil was calculated from the country-specific proportions of each HPV type in cervical cancer. Other clinical and cost inputs were specified of each of these two countries.

The time horizon of the optimization problem was one year, and the health/cost outcomes across the whole population were derived from the lifetime cohort results from the Markov model.

The model was run with a cohort of women over their lifetime for each one of the 52 scenarios described above separately for both countries. The results of each scenario were used to estimate the number of cervical cancer cases and total costs expected over 1 year at steady state for 100 000 women. The estimated number of cervical cancer cases (CC_i) and total costs (b_i) of each of the 52 prevention strategies were then used as input parameters for the optimization model.

Model validation

No validation effort was reported, neither for the health economic model nor for the optimization model.

Select optimization method

Due to relatively small size of the linear programming formulation described above (i.e., a total of 52 decision variables and 57 constraints), a standard primal simplex method was chosen to solve the problem.

Perform optimization/sensitivity analysis

This optimization problem was programmed in Microsoft Excel as a linear program and solved using the Solver Add-on (that uses the simplex method) to identify the optimal mix of the 52 cervical cancer prevention strategies to minimize the expected cervical cancer cases under a fixed budget, as well as screening and vaccination coverage constraints. The optimization model was solved twice using separate parameter sets reflecting the settings in UK and Brazil.

The base-case analysis assumed that the maximum screening coverage is the pre-vaccination coverage rate (65% in the UK and 50% in Brazil), maximum vaccination coverage was set to 80%, and the overall budget was the pre-vaccination budget allotted to screening and treatment of cervical lesions. No explanation was given as to why these maximum coverage rates were chosen in the base-case.

Sensitivity analyses were performed to understand the effect of altering the budget or the achievable screening or vaccination coverages (i.e., the constraints in the model) as well as the duration of vaccine protection (i.e., one of the parameters in the economic modeling). The budget constraint was varied from a 20% reduction to a 150% increase over the pre-vaccination levels, while the screening and the vaccination coverage levels were varied from 0% to 100%.

Report results

The optimal mix of strategies in the UK was 65% vaccination plus screening with a screening interval of 6 years, and 15% vaccination alone. In Brazil, the optimal mix was 50% vaccination plus screening with a screening interval of 5 years, and 30% vaccination alone. These optimal mixes of strategies would result in a reduction of cervical cancer by 41% in the UK and 54% in Brazil from pre-vaccination levels with no budget increase. It can be easily observed that in both countries, the optimal coverage rates for both preventive interventions are at the maximum levels permitted in the model.

In the sensitivity analyses, increasing the budget permits a shortening of the screening interval, but the effect on the reduction in cervical cancer cases is modest and tends to reach an early plateau. Vaccination alone (screening coverage set to 0%) could provide a reduction in cervical cancer cases compared with the pre-vaccination situation of screening alone with a lower budget. In both countries, the effect of reduced vaccine efficacy duration (25 years compared with lifetime) still results in a reduction in cervical cancer compared with the pre-vaccination strategy, but not as much as the base-case analysis. In both countries, a sharp reduction in the expected number of cervical cancers is seen when the vaccine coverage rate exceeds the maximum screening coverage rate or when screening coverage rate exceeds the maximum vaccine coverage rate while maintaining the budget (treatment and prevention) constraint.

Decision Making

In this case study, within the same budget, results of the optimization program show that it would be possible to substantially reduce the number of cervical cancer cases by implementing an optimal combination of HPV vaccination (80% coverage) and screening at pre-vaccination coverage (65% UK, 50% Brazil) while extending the screening interval to every 6 years in the UK and 5 years in Brazil.

Optimization models can be used to determine the optimal mix of primary and secondary prevention strategies minimizing cervical cancer burden under budget and logistic/infrastructure constraints. The key strength of optimization modeling is its ability to evaluate multiple combinations of different interventions and identify the mix that provides the maximum expected health benefit (reduction in cervical cancer cases) at the expected costs within the available budget. In addition, it allows the decision maker to set constraints reflecting local conditions, such as a limited available budget or limited achievable coverage rates.

In this paper, the optimization model uses the health economic model outcomes as its input parameters. Therefore, the validity of the optimization results is based on the validity of the health economic model. Furthermore, the implementation issues, such as how it will be decided who will receive vaccination, screening or both, were not discussed. In its current form, the optimization model is used more to demonstrate the potential value of adding vaccination strategy and to coordinate this addition with the existing screening practices in the UK and Brazilian health systems. For implementation purposes, a more advanced optimization model, as well as a more detailed health economic model that takes into additional considerations and interactions, (e.g. herd protection, resistance dynamics of the virus, transmission to the others, decreased secondary infections, infertility avoidance, logistic/infrastructure, socio-economic and equity concerns, etc.), are needed. Lack of these essential considerations in the economic and optimization models limits the usefulness of the results provided in the paper.

Case Study 2: Optimizing statin treatment initiation using MDP (Denton et al., 2009)

Problem Structuring

Type-2 diabetes (T2D) leads to many chronic outcomes, including stroke, coronary heart disease (CHD), kidney failure, etc. This study focuses on the selection of T2D patients for statin therapy of hypercholesterolemia. The market for statins is significant and remains burdensome to health system costs despite the availability of generics. Furthermore, there are a number of studies that report overprescribing (prescribing statins to those patients who only achieve marginal benefit) and under-prescribing (not prescribing statins to those patients most likely to benefit). Given this debate, Denton and colleagues' aim was to identify the optimal time to initiate statin treatment for hypercholesterolemia in T2D patients.

The problem is set up using an MDP framework. Traditional health services research methods focus on efficacy and/or cost-effectiveness at a snapshot in time to inform decisions, while MDP provides an in-depth modeling and understanding for optimal decisions at multiple time points over a patient's disease history. Due to the nature of the modeling, it provides the ability to personalize decisions, as opposed to one-size-fits-all policies and guidelines established for medical decisions. However, similar to other approaches, MDPs have assumptions based on data and/or the structure of the model.

Mathematical Formulation

The model optimizes a cost-reward function over time using a MDP. We recognize that MDPs are not commonly associated with constrained optimization because they typically do not have "constraints" in the same sense that the term is used in the mathematical programming literature (for example, in the previous case study). However, the ability of dynamic programming models to identify the optimal solution to the MDP (i.e., the optimal pattern of statin therapy initiation over time) provides an excellent example of a clinical use case for constrained optimization as long as one recognizes that constraints in a MDP are implicitly defined based upon allowable transitions between states and/or available decisions within each state. The structure of the model reflects shared decision-making by providers and patients over time as a function of patient age, patient clinical history, and several health states. History is dependent on CHD or stroke, as well as nine cholesterol levels pertaining to low, medium or high HDL and LDL levels. Patient information aligning with the data across three major heart studies provides much higher sensitivity to the proper time to initiate and maintain a statin regimen. The MDP model determines the optimal decision at each epoch, to maximize the overall rewards $v(s_t)$ while accounting for costs of all future states.

Reward function: $Max\ v(s_t) = E_{\underset{s}{\rightarrow}}[\sum_{t=1}^{T}\left(\lambda^{N^D t}\right) r(s_t, a(s_t))]\ \forall s_t \in \vec{S}$ where *t* is a time index for discrete decision epochs, s_t is an index for states at time period $t = 1, \ldots, \mathrm{T}$, $a(s_t)$ is the statin treatment decision at time $t = 1, \ldots \mathrm{T}$, $\lambda \epsilon [0,1]$ discounts the objective function depicting reduced value of rewards in future years, and N^D is the number of years in a decision epoch.

Reward function for each time period: $r\left(s_t, a(s_t)\right) = N^D\left[R(s_t) - \left(CF^S(s_t) + CF^{CHD}(s_t)\right) - a(s_t)C^{ST}\right] - \left[C^S\left(s_t, a(s_t)\right) + C^{CHD}\left(s_t, a(s_t)\right)\right]$ where N^D reflects the number of years in a decision epoch, $R(s_t)$ is the monetary value of quality adjusted life years, $C(S\mathrm{t})$ is the annual cost of statin treatment in period t, $CF^S(s_t)$ is the annual follow up care cost of stroke in period t, $CF^{CHD}(s_t)$ is the annual follow up care cost of CHD event in period t, $C^S(s_T)$ is the one time cost of stroke occurring in period *t*.

Reward function for final time period: $r\left(s_T, a(s_T)\right) = N^D\left[R(s_T) - \left(CF^S(s_T) + CF^{CHD}(s_T)\right) - a(s_T)C^{ST}\right] - \left[C^S\left(s_T, a(s_T)\right) + C^{CHD}\left(s_T, a(s_T)\right)\right] + E[PDHR|s_T, a(s_T)]$, where $E[PDHR|s_T, a(s_T)]$ is the post-decision horizon expected reward. The authors separate the time horizon into a decision horizon and a post-decision horizon. While the decisions are only made during the decision horizon, the rewards from the post-decision horizon still need to be included. For instance, while the decision to initiate statin therapy is only until age 80, the rewards of treatment after age 80, need to be included in the model.

Model Development

The starting age of the patients in the model was 40, and it was assumed that the patients could start statin treatment at any point between 40 and 80 in 2-year increments. If all these treatment options were modeled as separate scenarios, as is common in both clinical trials and economic evaluations, the problem would soon become quite complicated, especially if these treatment options were compared incrementally. However, using optimization techniques, one can identify a “single” optimal age for initiating statin treatment that maximizes the ‘reward’ function. The authors interpreted reward in terms of expected net monetary benefit E(NMB) as a function of quality-adjusted life years (QALYs), Cost and willingness-to-pay threshold (λ), that is:

$$E(NMB) = \Delta QALYs * \lambda - \Delta Cost \qquad (9)$$

Model Validation

The authors do not describe the model validation process, although it is clear from the Acknowledgements Section of the manuscript that the authors interacted extensively with experts within the clinical system where the research was conducted, as well as with external reviewers.

Select Optimization Method

The problem is set up using a Markov Decision Process (MDP). The MDP framework is intended for dynamic streams of decisions (i.e. decisions made over time). The time horizon and the time steps are identified as indices for decision epochs. Each decision in the stream guides the evolution of the system being modeled (typically the patient's health in medical applications) and may enable or foreclose further decisions. The patient's health is typically the state, and the decisions or actions are identified. MDPs can be considered as a hybrid between a Markov model and a decision tree.

Just as in Markov models, in an MDP, a patient's health state changes over time, transitioning from one discrete state to another according to a specified matrix of probabilities. However, typically in a Markov model, the decision maker has a choice between two or more treatment regimens to start the patient on initially. By contrast, in an MDP, the decision maker can make a choice about treatment in *every* time period. Thus, it is possible to model at a more granular level. At each time point, one may decide to start, stop or switch treatments, for as long as the patient survives. The constraints may involve the changes in states and/or the decisions. The transition from one state to another is characterized probabilistically.

In this study, the critical decision is when to start statins (starting statins is taken to be a one-time irreversible decision). Thus, in each time period from age 40 to death - or age 80 - there is a binary "start" or "delay" decision. Much of the complexity of the model is in the modeling of the health states. There are 324 health states describing various combinations of cholesterol and high-density lipoprotein levels (3 each), as well as stroke and CHD states (6 each).

Transition probabilities are parameterized based on a proprietary clinical database. The objective function is a combination of health sector costs (e.g., cost of treatment transacted between the provider, patient, and payer) and net monetary benefit, appropriately discounted over time. The risk of adverse events is modeled, for comparison through three third-party risk models.

Different risk-prediction models have estimated probabilities of T2D complications in patients based on sociodemographic and environmental risk factors. These predictive models can specify the type of treatment to reduce the risk of comorbidity. The most common validated risk models from several large studies are the United Kingdom Prospective Diabetes Study (UKPDS), the Framingham Heart Study (U.S.) and Archimedes, based on data trial results from the Heart Protection Study of 2002.

In particular, Denton et al. aimed to identify the optimal decisions for individual patients based on their attributes including age, gender, total cholesterol and high-density lipoprotein (HDL). The authors also performed the analyses using the predictions from each of the three risk models (i.e. UKPDS, Framingham, and Archimedes) as the choice of the risk model may impact the treatment decision, noting that it was likely that the predictions from the models could be different.

Performing optimization

The solution method is based on a backward induction approach starting with the last epoch T. Knowing the optimal future actions, the optimal decision at the current epoch can be established using recursive optimality in the following equation.

Recursive optimality: $v(s_t) = \lambda^{N^D} \max\left[r(s_t, a(s_t)) + \sum_{\forall s_{t+1}} p(s_{t+1}|s_t, a(s_t))v(s_{t+1})\right]$

Where $p(s_{t+1}|s_t, a(s_t))$ is the state transition probability at time t given state $s_t$and action $a(s_t)$

Decision variable: $a(s_t) = \begin{cases} 1\ if\ statin\ treatment\ is\ initiated \\ 0\ if\ statin\ treatment\ is\ delayed \end{cases}$

$$where\ if\ a_{t'} = 1, then\ a(s_t) = 1, \forall t > t'$$

Sensitivity Analysis

Where uncertainty in the model existed based on recommended statin starting therapy, the results of the optimization approach were tested for the low, medium and high cost of statins across willingness-to-pay threshold ranging from $25,000/QALY to $100,000/QALY in $25,000 increments. This additional analysis provides insight into the value of the model recommendations, and whether the recommendation results from using a low- or high-value proposition as a starting point. The model was also calibrated to best-available data from that time when statins did not have as much information on long-term effectiveness. Given that post-market knowledge of statin effectiveness is greater now than in 2009, these results express uncertainty where greater knowledge now exists.

Report Results

The model also unifies results across the UKPDS, Framingham, and Archimedes risk models, where there is noticeable variability in recommended treatment between studies. The Framingham model determines never to initiate statins for three of the nine metabolic states. The Archimedes risk model does not offer statin start points for all metabolic states, and predicts statin starting points based on statistical inference rather than by generalizable samples of patients, making the model prone to statistical error. In contrast, the UKPDS and Framingham risk models fit smoothed Weibull distributions across a well-defined population sample. The UKPDS and the Framingham model, give numerically different, but qualitatively similar optimal statin start time results. However, using the Archimedes risk model in the optimization did not produce a

smooth pattern for initiating statin therapy as observed with the UKPDS and Framingham models. The authors attribute this to "statistical error" associated with the Archimedes estimates.

The study demonstrates the value of the MDP framework, providing insight into when to start statin treatment. As one would expect, the model generally shows that statins should be started earlier for more severely ill patients. Exactly how early depends on the severity of the patient's condition but also on model parameters and which risk model is used. Interestingly, for less severe and elderly patients, from the results of Figure 2 in the article, it seems that it may not be worthwhile starting statin therapy at all. Women are in general recommended to start statin treatment later than men.

Decision Making

The study is an example of how the MDP modeling approach can provide personalized and clinically relevant recommendations (for patients of type *x*, start statins at age *y*) and integrate and compare different data sources and risk models. As there are many questions about the right time to start, stop and switch treatment in medical care, this seems an underused and highly promising framework for economic evaluation.

Traditional health services research methods focus on efficacy and/or cost-effectiveness at a snapshot in time to inform decisions, MDP provides an in-depth modeling and understanding for optimal decisions at multiple time points over the patient's disease history. Due to the nature of the modeling, it provides the ability to personalize decisions, as opposed to one-size-fits-all policies and guidelines established for medical decisions. However, similar to other approaches, MDPs have assumptions based on data and/or the structure of the model. Once the results are obtained, sensitivity analyses can be performed (e.g., for some range of variation in the transition probabilities). Once satisfied with the solution, translation is in the form of guidelines and/or decision tools. Owing to the modeling and computational nature of the MDPs, they can easily be translated into decision support systems to use in practice.

This example showed the use of MDP for optimizing the start time of statin therapy. MDPs can be used for other similar decision-making problems for breast or prostate cancer screening, the decision for biopsy, initiating HIV therapy treatment policies, etc. The underlying theme is focusing on decisions over time, with decisions at one point affecting future states and decisions operating under constrained resources. The results of the optimization models can help establish optimal clinical guidelines (Steimle and Denton 2017)

Educational Case Study: Optimizing the Delivery of Radiation Therapy to Cancer Patients (Shepard et al., 1999)

We now challenge the reader to try their hand at formulating alternative models designed to optimize radiation therapy using the steps outlined in Table 1. The discussion and modeling approach closely follow the seminal work by Shepard et al. (1999). A simplified version of the originally published mathematical notation and formulations are provided in the appendix for the readers to check their formulations. Model formulation is often the most challenging part of applying constrained optimization methods, and successful applications typically result from multidisciplinary collaboration, involving domain experts on the subject matter as well as the modeler. Therefore, one should not feel disappointed if the model specifications do not exactly match those provided in the appendix.

There are two main reasons for the selection of radiation treatment planning as the educational case study. First, the problem statement is relatively simple to express, and so it is a helpful example to showcase several different constrained optimization models (e.g., linear, nonlinear, mixed integer). Second, while the problems presented in this educational case study are typically studied by operations researchers and medical physicists, the parameters defining treatment goals and constraints heavily rely on the health outcomes research findings comparing the effectiveness of various cancer treatment protocols and modalities in different patient populations. Therefore, we believe that awareness of these treatment planning models can lead to new research directions in health outcomes and observational cohort studies. One such initiative is the Oncospace (Bowers et al., 2015), the main goal of which is to create a learning health system that systematically collects relevant clinical data and predicts potential outcomes for specific patient characteristics and treatment plan parameters (Chen et al., 2016, McNutt et al., 2016). These learning health systems hold the promise of substantially improved outcomes for all patients.

Shepard et al. (1999) presented several constrained optimization models for the intensity-modulated radiation therapy (IMRT) treatment planning problem. In this setting, a cancerous tumor within a patient's body is targeted with several beams of radiation passing through the tumor from different directions since a single beam of radiation strong enough to control the growth of the tumor would do unacceptable damage to healthy tissue in its path. A typical objective function in this setting might be to maximize the portion of the tumor region receiving a dose of radiation sufficient to prevent further tumor growth while a constraint might be ensuring that healthy tissue does not receive damaging levels of radiation dose. The decision variables might be the angles at which the beams are positioned (Craft, 2007) or the intensity of the subcomponents of beams, referred to as beamlets (Romeijn et al., 2006). Although the fundamental problem sounds straightforward in principle, accurately solving it presents substantial conceptual and computational challenges (Bortfeld, 2006, Sir et al., 2012, Akartunalı et al., 2015).

Background

IMRT involves radiation sources (photons or protons) outside the body (Purdy et al., 2012). Several modeling techniques have been proposed to optimize IMRT considering the complicating factors such as 1) the underlying physics and biology; 2) conflicting treatment goals; 3) uncertainties caused by daily setup procedures; 4) organ motion and 5) ensuring that the results and facts garnered in the course of treatment are efficiently integrated into the treatment plan.

In clinical practice, radiation therapy is delivered over a period of time as a series of small dosages called "fractions." Dose delivery in each of these treatment sessions is optimized in order to both increase tumor control probability (TCP) and decrease damage to the healthy tissue surrounding the tumor by giving it time to recover (Thames and Hendry, 1987). Several realistic dose models have been proposed that reflect the radiobiological effects of fluctuations in dose delivery over fractions (Bortfeld and Paganetti, 2006, Fowler, 1989). These models are used to develop biological indices that can accurately predict the clinical outcome of radiation treatment, such as equivalent uniform dose (EUD), TCP, and normal tissue complication probability (NTCP) (Song et al., 2004).

Developing a treatment protocol is complicated - taking multiple considerations into account. Randomized control trials and retrospective studies are effective ways of determining the efficacy of various treatment protocols. Furthermore, while treatment protocols are designed for specific cancer types and patient populations, each patient has unique characteristics, comorbidities, tumor location and size, and proximity of tumor region to organs-at-risk (e.g., rectum in the case of prostate cancer) and normal tissue. Therefore, radiation therapy treatment plans must be optimized to ensure that the treatment protocol requirements are satisfied for each patient. The remainder of this section will focus on IMRT treatment planning. Similar models can be used for other radiation therapy modalities as well.

The steps in the optimization checklist will be followed below. In each step, we will provide necessary background information first and then ask the reader questions related to important aspects of that step. We will provide sample answers to some questions to assist the reader with the modeling exercise.

Problem structuring

Decisions in radiation treatment planning involve determining the intensity of modulated beams and the amount of dose delivered to various points in and around the tumor region. The treatment protocol, prescribed by a radiation oncologist, specifies treatment objectives and constraints. For example, according to a prostate cancer randomized control trial (RCT) conducted by Pollack et al. (2002), delivering 78 Grays of radiation dose to a prostate tumor results in substantial improvement in tumor control. However, the higher doses also increase complications in the rectum, which is an organ-at-risk that needs to be protected from high doses. Using these findings as part of a treatment protocol, consider how you would design the objective function to ensure that most of the tumor region receives 78 Grays of radiation dose.

Think about these two possibilities:

1. For every point in the tumor region, you can calculate the difference between the actual dose and the prescribed target dose, i.e., 78 Grays. You can describe an objective function that minimizes the largest difference as follows: *Minimize the maximum difference between the actual and prescribed target doses across all points in the tumor region.*
2. Suppose that the radiation oncologist is OK with a small difference (e.g., 2 or 3 grays) but wants to avoid large differences (e.g., 10 Grays) from the target dose in the tumor region. Similar to the definition above, describe an objective function in such a way that the more the dose difference at a certain point in the tumor region from the target dose; the more penalty is accrued. Hint: a square of the dose differences can create the desired effect.

Further, how would you impose constraints on dose delivered to the rectum region to avoid complications? Again, consider two possibilities:

1. The radiation oncologist wants to provide overall protection by keeping the dose anywhere in the rectum region below 30 Grays. You can define a constraint to this effect as follows: *The dose at any point in the rectum must be less than 30 Grays.*
2. According to the results from the randomized control trial by Pollack et al. (2002), dose escalation results in better outcomes for prostate cancer patients if the portion of the rectal volume receiving 70 Grays or more dose can be kept below 25%. How do you define a constraint that ensures this?

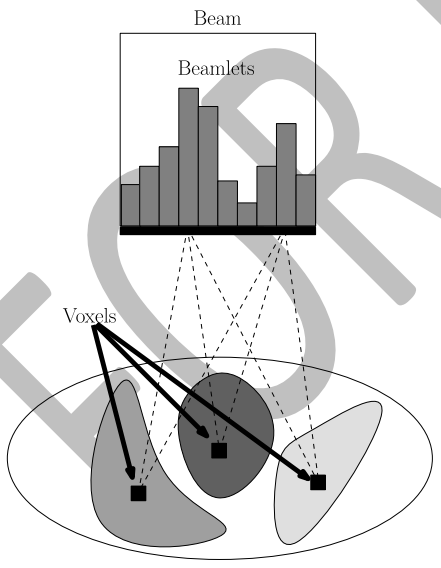

Figure 1: Discrete representation of patient anatomy. Patient anatomy is discretized into voxels, and treatment beams are discretized into beamlets.

Mathematical formulation

For IMRT optimization, voxels, which are volume elements on a rectilinear grid in a three-dimensional space (this is analogous to a pixel in three-dimensional space), are identified in the anatomy of a patient undergoing radiotherapy (see **Error! Reference source not found.**). The radiation fields are modulated using a multi-leaf collimator (MLC) (Alber and Nüsslin, 2001). Therefore, the radiation beams are regarded as being comprised of many ``beamlets'' (see **Error! Reference source not found.**). Once voxels and beamlets are determined, a dosimetrist calculates how much dose a beamlet of unit intensity can deliver to a voxel.

Parameters:

Given these descriptions, think about what parameters are needed to formulate an optimization model for IMRT. For example, it may be convenient to introduce notation V_t, V_o, and V_h to denote the set of the tumor, organs-at-risk (OAR), and healthy tissue voxels, respectively. One parameter is the prescribed target doses of the tumor voxels:

τ_i *is the target dose for tumor voxel* $i \in V_t$.

Now, try to define notation for the following parameters:

- An upper limit on dose delivered to an organ-at-risk voxel.
- The dose delivered to a specific voxel by a specific beamlet with unit intensity.

What other parameters are needed? Compare your parameter definitions with those provided in the appendix.

Decision Variables:

There are two sets of decision variables: 1) the intensity of each beamlet; 2) the dose delivered to each voxel.

Introduce notation to define these variables. Compare your variable definitions to those in the appendix.

Objective function and constraints:

How can you combine these parameters and decisions variables to define an objective function and constraints? (Refer to your definitions from the problem structuring step.)

The specific choice of objective functions and constraints described above will ultimately determine the type of constrained optimization model. For example, think about whether a simple linear function can be used to model the first objective of minimizing the largest difference from a target dose. What type of mathematical function (see the hint provided above) can be used to model an objective function that penalizes larger differences from the target dose more? Linear or non-linear?

After attempting to formulate the IMRT optimization problem, compare your formulation with the ones in the appendix.

Advanced considerations:

If a radiation oncologist is only concerned with limiting the amount of dose delivered to a certain region, you can simply use a continuous decision variable representing dose delivered to that region and constrain it to be below the desired threshold. If, however, the radiation oncologist is interested in sparing only a portion of an organ (i.e., the second constraint possibility described in the problem structuring step), then think about what additional (possibly binary) variables you need to model this constraint.

Compare your new variable and constraint definitions to the alternative formulations provided in the appendix.

Model development

In this step, the treatment planner implements the model formulation using treatment planning software and specialized optimization solvers. The treatment planner makes various decisions regarding model parameters and structure. For example, the treatment planner chooses the density and location of the voxels to provide a good approximation of the regions of interest specified in the treatment protocol. The number and positions of the beams that will deliver radiation to the patient are also chosen based on the geometry of the patient's anatomy and treatment strategy specified in the protocol. Depending on the location of the tumor, an appropriate radiation physics software needs to be used to calculate the dose delivered to a voxel from a unit-intensity beamlet. Once all parameters are specified, the model formulation is populated with actual parameter values and translated into computer code to communicate with an optimization solver.

Model validation

The treatment planner goes through several steps to ensure that the model accurately represents the patient's anatomy and radiation physics. Robustness of the optimization parameters determined in the model development step must be verified in the presence of various uncertainties caused by organ motion, setup uncertainty, and potential structural changes to the patient's anatomy during the treatment course. For example, multiple dose deposition matrices may need to be calculated for different scenarios involving setup errors.

Select optimization method

Selection of the optimization method depends on the model structure and various computational considerations depending on the tumor site. The treatment planner must make a trade-off between the treatment plan quality and computational time required to obtain it. For example, the mathematical formulation of a complex case requiring protection of certain portions of several critical organs in the neighborhood of the tumor region might result in a complex mixed-integer programming model. Solving such a model to optimality might take multiple hours, making it clinically intractable. In this case, the treatment planner may be forced to either change the model structure by making certain simplifying assumptions or keep the original mixed-integer programming model but use a heuristic method (instead of an exact solution algorithm such a branch-and-bound) to obtain a good (but not necessarily optimal) solution in a reasonable amount of time.

Perform optimization/sensitivity analysis

Optimization of radiation therapy is an iterative process. After solving the mathematical formulation, the treatment planner reports the results to the radiation oncologist, who then considers several trade-offs between conflicting goals of controlling tumor vs. sparing healthy tissue and critical organs. In each iteration, the treatment planner makes changes to the model parameters and sometimes to the structure of the model. For example, if the radiation oncologist wants to “cool down” the rectum in order to avoid complications, the treatment planner might lower the limit on the dose delivered to the rectum. The changes made to the model structure may require switching to a different optimization method (compare different optimization models and their underlying requirements described in the appendix).

The authors of the case study systematically changed various essential parameters, including bounds on dose delivered to different regions, objective weights associated with different regions, number of beam angles, and relative size of the protected portion of an organ-at-risk.

Report results

Following the optimization process, the treatment planner presents the solutions to the radiation oncologists. Typically, multiple solutions, obtained through the iterative optimization process, are reviewed. The comparisons between these solutions are made using various dose-volume histograms, iso-dose curves, and dose distribution heat maps (Barrett et al., 2009). The authors of the case study also used these visualization methods to compare the quality of various treatment plans obtained by different optimization models.

Decision making

After reviewing multiple solutions and considering various trade-offs between conflicting treatment goals specified by the protocol, the radiation oncologist chooses a treatment plan, which is then delivered in multiple treatment sessions.

Discussion

A substantial portion of cancer patients undergoes radiation therapy at some point during the course of their disease (Miller et al., 2016). Optimization models help to make tradeoffs between conflicting criteria specified by the treatment protocol and achieve best outcomes for an individual patient.

This last case described various steps in the optimization checklist to formulate and solve an optimization model for the radiation therapy treatment planning problem. The case also illustrated how a given problem could be formulated as a linear program, non-linear program, or mixed integer program. Further details including the advantages and disadvantages of each approach are explained in the appendix to provide a learning opportunity for the reader.

6. Conclusion

This is the second report by the ISPOR Constrained Optimization Methods Emerging Good Practices Task Force. The primary objective is to provide an overview of areas where optimization methods can be applied and describe three case studies illustrating the application of constrained optimization methods to critical clinical and health policy questions. The cases illustrate several of the major variants of constrained optimization methods and demonstrate the potential of these methods in complementing classical economic evaluation decision-making framework. In the first case study, linear programming methods were used to identify the optimal mix of HPV vaccination and screening to minimize the number of cervical cancer cases subject to a budget constraint. Similarly, in the second case study, MDP and dynamic programming were used to identify the optimal time to initiate statin therapy in type-2 diabetes patients. The first two case studies describe the translation of the original problem into its mathematical formulation, its estimation, interpretation, and use. In contrast, the third is an educational case that allows the reader to work through the formulation of a constrained optimization problem using the ISPOR Optimization Good Practice Guidelines Checklist.

The healthcare sector faces major challenges with regards to appropriate diagnosis and treatment, allocation of scarce resources, designing policies, etc. Constrained optimization methods provide an approach for finding optimal solutions to complex problems in the face of constraints. As such, they are

790 complementary to and build on the health economic models and simulation methods that are widely used to
791 guide clinical and policy decision making.

792 Constrained optimization methods can improve the current reimbursement decision-making processes,
793 which take the budget constraints partially into account. In the constrained optimization framework, budget
794 constraints can be incorporated explicitly, together with other types of constraints like human resource or
795 geographical equity constraints. In addition, when there are numerous treatment options available for
796 treating patients with a specific condition constrained optimization might prove to be an efficient method for
797 developing treatment protocols or guidelines compared to the classical economic evaluation framework.

798 In the current healthcare landscape health economic modeling is widely used to make reimbursement
799 decisions for new technologies (particularly outside the United States). Constrained optimization methods
800 can help decision-makers incorporate related considerations beyond the reimbursement decision itself
801 including the best way to integrate the new technology with the health-care delivery system, as well as in
802 technology disinvestment decisions. These are becoming crucial as personalized medicine and
803 performance-based payment concepts become more common.

804 It is important to recognize that application of constrained optimization methods in healthcare is still an
805 emerging area and there are some challenges that must be addressed. Constrained optimization methods
806 can be limited by data availability and quality, and validating an optimization model can be
807 challenging. Choosing and applying the appropriate method can be difficult and require specific expertise.
808 Interpreting results and knowing which solution algorithm is likely to be best requires a level of
809 methodological understanding and sophistication. However, despite these challenges, the application of
810 constrained optimization methods to health care decision making offers substantial potential benefits which
811 make them a valuable addition to the arsenal of analytic methods at the disposal of the researcher.
812 Approaching a problem in the context of mathematical optimization forces modelers to identify and quantify
813 the endpoint that they are trying to accomplish. But most importantly, constrained optimization takes into
814 account the limits placed on the solution by real-world factors such as budgets, availability of treatments,
815 staffing capacity, and patient characteristics. As a result, the identified optimal solution is much more likely
816 to be feasible to implement. In a disease management problem, by treating patients optimally, we have the
817 potential to improve population health and enhance the value associated with health care expenditure. For
818 individual patients, this means providing treatment with the proper therapy faster. For physicians, this can
819 help provide optimal health outcomes for their patients, enhance the performance of their medical practice,
820 and offer more efficient health care delivery. The task force hopes that these two reports will encourage
821 modelers to explore the use of optimization methods and looks forward to seeing more published
822 optimization applications and the development of further guidelines and resources as the use of these
823 methods becomes more widespread.

824

825

Appendix: Model formulations for Case 3

In this section, we guide the reader through the formulation process for the optimization of IMRT.

Parameters:

- V_t, V_o, and V_h are the set of tumor, organs-at-risk (OAR), and healthy tissue voxels and V is the set of all voxels. n_t, n_o, and n_h are the number of voxels in corresponding regions and n is the number of all voxels.
- B is the set of beamlets and by w_j the intensity of beamlet $j \in B$. m is the number of all beamlets.
- D is the $n \times m$ dose deposition matrix, generated by simulating how an X-ray particle deposits energy as it travels through the body of the patient. D_{ij} is an element of D representing the dose delivered to voxel i by beamlet j when its intensity is set to unit intensity.
- τ_i is the target dose for tumor voxel $i \in V_t$.
- l_t and u_t are the lower and upper bounds on dose delivered to tumor voxels, respectively.
- u_o and u_h are the upper bounds on dose delivered to OAR and healthy tissue voxels, respectively.

Decision Variables:

- w_j is the intensity of beamlet $j \in B$.
- d_i is the dose delivered to voxel $i \in V$.

Objective function:

- $f(d; \tau)$ is the treatment objective function where d is the vector of doses delivered to each voxel and τ is the vector of ``target'' doses for each voxel, as specified by the treatment protocol. Several forms of treatment objective functions have been proposed in the literature. As described above, one possibility is minimizing the maximum deviation from the tumor target dose specified by the treatment protocol:

$$f(d;\tau) = \min_{w} \max_{i \in V_t} |d_i - \tau_i|$$

Linear Programming Formulation:

The IMRT optimization problem can be formulated as a linear program (LP) with the above objective function:

$$\text{Min} \quad \max_{i \in V_t} |d_i - \tau_i| \tag{1}$$

$$\text{subject to} \quad d_i = \sum_{j \in B} w_j D_{ij}, \quad \forall i \in V \tag{2}$$

$$l_t \leq d_i \leq u_t, \ \ \forall i \in V_t \tag{3}$$

$$d_i \leq u_o, \ \ \forall i \in V_o \tag{4}$$

$$d_i \leq u_h, \ \ \forall i \in V_h \tag{5}$$

$$\sum_{i \in V_o} d_i \leq n_o \beta \tag{6}$$

$$w_j \leq \frac{\alpha}{m} \sum_{k \in B} w_k, \ \ \forall j \in B \tag{7}$$

$$w_j \geq 0, \ \ \forall j \in B \tag{8}$$

Even though the objective function (1) is nonlinear, it can easily be converted to equivalent linear function by simple variable transformations. Constraint set (2) defines the relationship between dose delivered to each voxel and beamlet intensities. Constraint sets (3)-(5) restrict maximum and minimum dose received at various treatment regions. Constraint (6) limits mean dose delivered to OAR to be lower than a predetermined constant β. Constraint set (7) ensures that the ratio between maximum and average beamlet intensity does not exceed a predetermined constant α in order to avoid extremely high dose regions in patient anatomy. Finally, constraint set (8) ensures beamlet intensities in the optimal solution are positive.

Nonlinear Programming Formulation:

Instead of penalizing the maximum deviation from the target dose, the radiation oncologist may want to avoid any significant deviations from the target dose. In this case, we can construct an objective function with a quadratic penalty for deviating from the target dose.

$$f(d;\tau) = \min_{w} r_t \sum_{i \in V_t} (d_i - \tau_i)^2 + r_o \sum_{i \in V_o} (d_i - \tau_i)^2 + r_h \sum_{i \in V_h} (d_i - \tau_i)^2, \tag{9}$$

where r_t, r_o, and r_h are weights associated with corresponding regions representing their relative importance. The target dose for OAR and healthy tissue is typically zero, meaning that any dose delivered is penalized. These weights are determined through an iterative process between the treatment planner and radiation oncologist in quest for finding the right trade-off between multiple conflicting treatment criteria specified by the treatment protocol. A nonlinear programming model can be obtained by replacing objective function (1) with (9).

Mixed-integer Programming Formulation:

As mentioned above, according to the results from the randomized control trial by (Pollack et al., 2002), dose escalation results in better outcomes for prostate cancer patients if the portion of the rectal volume

receiving 70 Grays or more dose can be kept below 25%. These types of requirements in treatment protocols are referred to as dose-volume constraints representing the willingness of radiation oncologist to sacrifice a portion of an organ-at-risk to improve tumor control. Dose-volume constraints can be introduced by defining binary variables that indicate whether the dose to each voxel in the region of interest is above a certain value (e.g., λ). For example, we can define the binary variable for a dose-volume constraint on an OAR, which constrains number of voxels in the OAR receiving a dose higher than a specified value, as follows:

$$x_i = \begin{cases} 1, & \text{if } d_i \geq \lambda \\ 0, & \text{otherwise} \end{cases}, \quad \forall i \in V_o \tag{10}$$

The dose-volume constraint can then be formulated as follows

$$d_i \leq u_o + M x_i, \quad \forall i \in V_o, \tag{11}$$

$$\sum_{i \in V_o} x_i \leq \delta n_o, \quad \forall i \in V_o, \tag{12}$$

where δ is the specified percentage and M is an appropriately large number.

The variables defined in (10) are required to be binary, which substantially increases computation time to find the optimal solution compared to the LP formulation in (1)-(8).

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